The Stereochemistry of Rigid [2.2]Paracyclophanylphenonium Ions. The Formolysis of the *exo* and *endo* Isomers of 17-Tosyloxymethyl-4,5-tetramethylene[2.2]paracyclophane[1]

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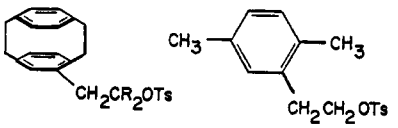
Abstract: The formolysis rates of the *exo*-(**5a**) and *endo*-17-tosyloxymethyl-4,5-tetramethylene[2.2]paracyclophane (**5b**) have been measured. Both of these solvolyses involve participation by the paracyclophane moiety. Comparison of the rates show that *exo*-carbonium ion formation is preferred. Product analysis shows that bridged ions may be involved and that neutralization by the incoming nucleophile occurs at the *exo* electron-deficient carbon in the bridged ion.

Earlier investigations have shown that [2.2]paracyclophanyl is a better neighboring group than phenyl. Thus, 2-([2.2]paracyclophanyl)ethyl tosylate (**1a**) undergoes acetolysis six times faster than 2-(2,5-dimethylphenyl)ethyl tosylate (**2**)[2] and 18 times faster than



1a R=H
1b R=D

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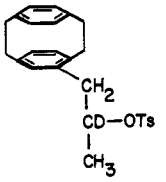
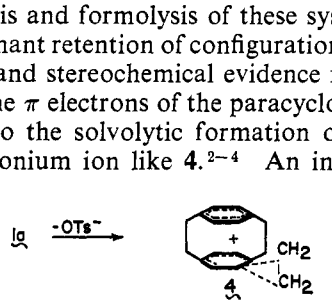
2-phenylethyl tosylate.[3] Recent solvolytic studies of the diastereomeric tosylates **3**α and **3**β have shown that



3a and **3β**

the acetolysis and formolysis of these systems proceeds by predominant retention of configuration.[4] Thus both the kinetic and stereochemical evidence require participation by the π electrons of the paracyclophanyl moiety and point to the solvolytic formation of a paracyclophanylphenonium ion like **4**.[2-4] An interesting question arises concerning the stereochemistry of paracyclophanylphenonium ions. Cram and Singer[2] found that the acetolysis of deuterated 2-([2.2]paracyclophanyl)-ethyl tosylate (**1b**) gives a product in which no deuterium scrambling is observed; therefore, the phenonium ion is exclusively formed from and neutralized at either the *exo* or *endo* electron-deficient methylene group. Two isomeric phenonium ions and solvolytic pathways are possible with **1b**. It has usually been argued that the



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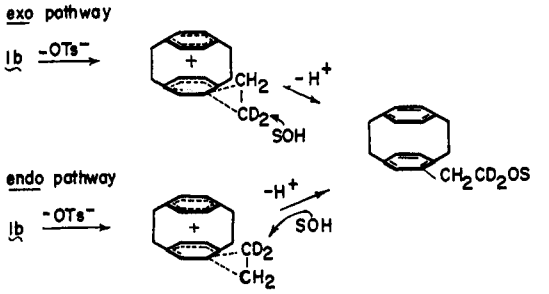
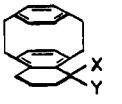


exo pathway is preferred.[2,4] The formolysis rates of *exo*-(**5a**) and *endo*-17-tosyloxymethyl-4,5-tetramethylene[2.2]paracyclophane (**5b**) and the structures of the



5a X=H, Y=CH_2OTs
5b X=CH_2OTs, Y=H

6a X=H, Y=CH_2OH
6b X=CH_2OH, Y=H

solvolysis products were investigated to determine the stereochemical relationships involved during the formation and neutralization of paracyclophanylphenonium ions. The results of these studies are the subject of this paper.

Results

The stereospecific syntheses of the *exo* and *endo* alcohols **6a** and **6b** have previously been described.[5] The

(1) Abstracted from the Ph.D. Thesis of T. Vigo, Tulane University, 1969.
(2) D. J. Cram and L. A. Singer, *J. Amer. Chem. Soc.*, **85**, 1075 (1963).
(3) D. J. Cram, *ibid.*, **86**, 3767 (1964).
(4) D. J. Cram and F. C. Harris, Jr., *ibid.*, **89**, 4642 (1967).
(5) M. J. Nugent and T. L. Vigo, *J. Org. Chem.*, **34**, 2203 (1969).

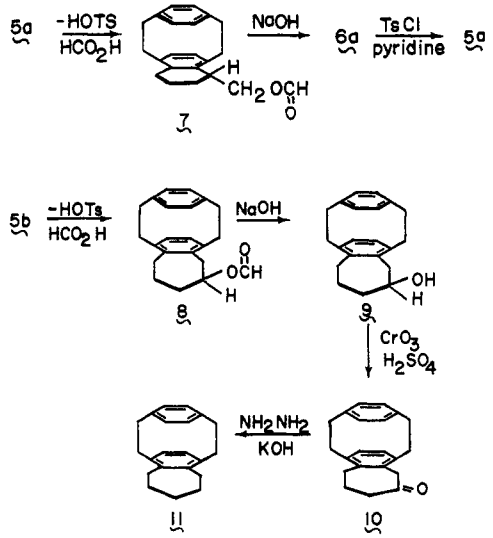
tosylates were prepared by the usual method from tosyl chloride and pyridine, and their formolysis rates were measured conductometrically.[6] Because of the limited solubility of **5a** and **5b** in anhydrous formic acid, it was necessary to dissolve the tosylates in 25 μl of reagent grade methylene chloride prior to adding 1 ml of formic acid. The resulting formic acid solutions, which were used for rate measurements, were 0.01 M in tosylate.[7] The rate plots were linear through three to four half-lives. Good straight lines were obtained in all cases and no drift in the infinity conductance was observed after ten or more half-lives. The kinetic data are shown in Table I.

Table I. Formolysis[a] Data for *exo*- and *endo*-17-Tosyloxymethyl-4,5-tetramethylene[2.2]paracyclophane

Compd	Temp, °C	$k \times 10^3$ sec^{-1}	$\Delta H^{\ddagger}$, kcal	$\Delta S^{\ddagger}$, eu
5a[b]	36.37	9.50 ± 0.50	18.9	−6.87
	44.65	21.7 ± 0.1		
5b	36.37	1.31 ± 0.02	21.7 ± 0.6	−1.78
	47.34	4.79 ± 0.18		
	58.40	14.6 ± 0.3		

[a] Formic acid containing 2.5 vol % methylene chloride. [b] Because of the low solubility of **5a** in formic acid containing 2.5 vol % methylene chloride, it was not possible to measure formolysis rates for this compound at temperatures below 36°. Because of the fast formolysis rate, rate measurements above 45° were not possible.

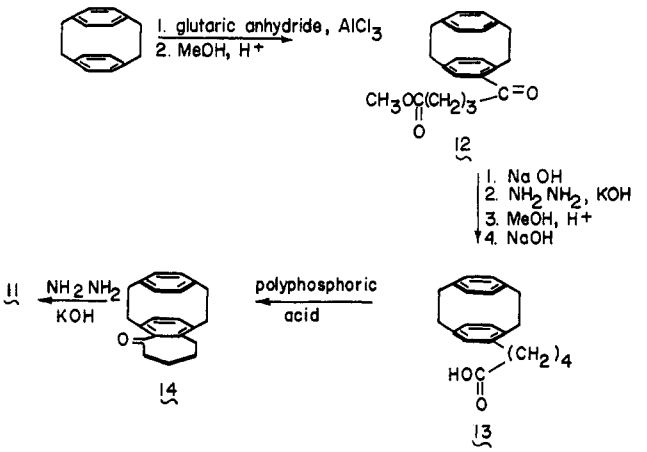
Formolysis products were isolated from solvolysis mixtures after ten half-lives. Control experiments showed that the presence of excess sodium formate in these solvolysis mixtures did not affect the yields or the structures of the products obtained. The formolysis experiments and the identification of products was carried out as shown below.



In the case of the *exo*-tosylate **5a**, a single formate **7** (mp 109–110° from ether–pentane) was obtained in 96% yield. The structure of this formate can be assigned from the following evidence. Saponification with sodium hydroxide gave *exo*-17-hydroxymethyl-4,5-tetramethylene[2.2]paracyclophane (**6a**), mp 116–119° (lit.[5] mp 118–121°). The nmr and ir spectra of the alcohol were very nearly superimposable with those of authentic material. Because of the difficulty encountered in further purification of small amounts of this alcohol, it was converted to the starting tosylate **5a**, mp 116–121°, mmp 116–121° with authentic sample. Thus the formolysis of **5a** proceeds without rearrangement.

Formolysis of *endo*-tosylate **5b** produced a single formate **8** in 98% yield, mp 136–137° from ether–pentane. Saponification of this formate followed by chromatography on grade III neutral alumina and crystallization from hexane–acetone produced alcohol **9**, mp 129–130°.

Alcohol **9** gave a single ketone **10** (mp 122–124°) on oxidation with chromium trioxide–sulfuric acid in ether. Wolff–Kishner reduction of this ketone produced 4,5-pentamethylene[2.2]paracyclophane (**11**). This structure was confirmed by synthesis of an authentic sample of **11** as shown below.



Discussion

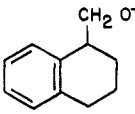
The relative formolysis rates of tosylates **5a** and **5b** together with the relative rate of 1-tosyloxymethyltetralin (**15**)[8] are shown in Table II. That the formolysis

Table II. Relative Formolysis Rates of Tosylates at 36.37°

Compd	k_{rel}
15	1[a,b]
5b	17[c]
5a	125[c]

[a] Extrapolated from data at other temperatures. [b] Anhydrous formic acid. [c] Anhydrous formic acid containing 2.5 vol % methylene chloride.

of **15** involves participation by the π electrons is shown by the fact that it solvolyzes 220 times faster than cyclohexylcarbinyl tosylate.[8] Since both the *exo*-tosylate **5a** and the *endo*-tosylate **5b** undergo formolysis at rates greater than that of tosylate **15**, the formolysis of **5a** and



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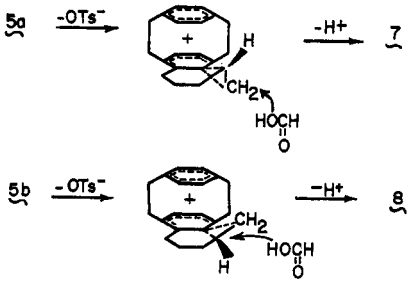
(6) (a) S. Winstein, M. Brown, K. C. Schreiber, and A. H. Schlesinger, *J. Amer. Chem. Soc.*, 74, 1140 (1952); (b) P. D. Bartlett, S. Bank, R. J. Crawford, and G. H. Schmid, *ibid.*, 87, 1288 (1965); (c) S. C. Cherkovsky, Ph.D. Thesis, Harvard University, 1966.

(7) Control experiments with *anti*-7-norbornenyl brosylate have shown that the acetolysis rate is retarded by about 10% when acetic acid containing 2 vol % chloroform is used rather than pure anhydrous acetic acid: P. D. Bartlett and M. J. Nugent, unpublished results.

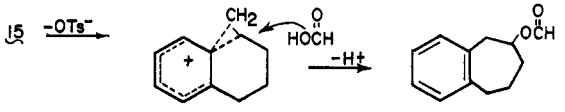
(8) R. Huisgen, G. Seidl, and I. Wimmer, *Tetrahedron*, **20**, 623 (1964).

5b must involve participation by the π electrons of the paracyclophane moiety. The fact that the *exo*-tosylate **5a** solvolyzes seven times faster than the *endo*-tosylate **5b** reflects the preference for *exo*-carbonium ion formation in these rigid systems. Examination of models of tosylates **5a** and **5b** shows that for steric reasons the tosylate group of the *endo* isomer **5b** must adopt a conformation in which it is *anti* to the paracyclophane moiety. This *anti* conformation of **5b** is extremely favorable for backside participation by the π electrons of the paracyclophane ring. Models show there is no similar conformational preference in the *exo* isomer **5a**. The conformational advantage of the *endo* isomer is reflected in its larger entropy of activation (Table I). In spite of this conformational advantage of **5b** the *exo*-tosylate **5a** undergoes formolysis at a greater rate than **5b**. We estimate that the preference for *exo*-carbonium ion formation in the [2.2]paracyclophanylethyl systems **1** is reflected by the difference in activation enthalpies of tosylates **5a** and **5b** of 2.8 kcal or a rate factor of 100 at 40°.

The formolysis of **5a** gives a high yield of formate **7** which shows no skeletal rearrangement. The formolysis of **5b** gives a single formate **8** in high yield in which ring expansion has occurred. The fact that a single formate **8** is isolated in this case provides evidence for a bridged-ion intermediate in this system since an open carbonium ion should lead to an epimeric pair of *endo* and *exo* ring-expanded formates. Mechanisms involving phenonium ion intermediates in these systems can be written as



The formolysis of tosylate **15** leads exclusively to ring expansion *via* the mechanism



This result is not surprising in view of earlier results concerning phenonium ions where the aryl group is bridged between secondary and primary carbon atoms.[6a,9] In such cases solvent attack on the bridged ion occurs exclusively at the secondary carbon atom since this carbon atom is best able to support positive charge. In the paracyclophanyl tosylates **5a** and **5b** solvent attack does not always occur at the secondary carbon atom; rather the site of solvent attack is governed by the stereochemistry of the bridged carbon atoms. Solvent attack occurs in both cases at the *exo* electron-deficient, bridged carbon atom. In the case of the ion derived from **5a** *exo* attack cannot lead to skeletal rearrangement; however, in the case of the ion derived from **5b** *exo* attack results in complete and stereospecific rearrangement to the ring-expanded formate **8**. We tentatively assign the *endo* configuration to **8** on the basis of the above arguments.

Both steric[2] and electronic[4] effects have been cited as reasons for *exo*-carbonium ion formation and neutralization in [2.2]paracyclophane systems. A rate-enhancing steric effect such as "B strain" [10-12] is not predominant in the formolysis of **5b**. Such strain would be relieved as the tosylate group in the *endo* isomer **5b** leaves. In such a case one would expect a rate enhancement for **5b** relative to **5a**. We are not able from the present data to eliminate rate-retarding steric effects such as steric hindrance to solvation[13-15] in the case of the *endo*-tosylate **5b**. Further work to elucidate the reasons for the observed stereochemistry is in progress in these laboratories.

Experimental Section

General. All melting points and boiling points are uncorrected. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

***exo*-17-Tosyloxymethyl-4,5-tetramethylene[2.2]paracyclophane (5a).** To a cold (0°) solution of 0.585 g (2.0 mmol) of *exo*-17-hydroxymethyl-4,5-tetramethylene[2.2]paracyclophane (**6a**) in 2.5 ml of pyridine was added 0.585 g (3.0 mmol) of *p*-toluenesulfonyl chloride. After 22 hr at 0° the reaction mixture was poured into ice water. The reaction mixture was extracted three times with methylene chloride. The methylene chloride solution was then washed with water, 5% hydrochloric acid, and water. The methylene chloride solution was dried over sodium sulfate and evaporated at 0°. The resulting oil was dissolved in petroleum ether (bp 30–60°)–ether from which it crystallized to give 0.42 g (48%) of white crystals, mp 116–121° dec. Two recrystallizations from petroleum ether–ether gave an analytical sample, mp 110–111° dec.

Anal. Calcd for $C_{28}H_{31}O_3S$: C, 75.30; H, 6.77; S, 7.17. Found: C, 75.18; H, 6.68; S, 7.27.

***endo*-17-Tosyloxymethyl-4,5-tetramethylene[2.2]paracyclophane (5b)** was prepared in a manner similar to **5a**. The tosylate was obtained in 47% yield, mp 115–116 from petroleum ether–ether.

Anal. Calcd for $C_{28}H_{31}O_3S$: C, 75.30; H, 6.77; S, 7.17 Found: C, 75.22; H, 6.75; S, 7.20.

Kinetics. Formic acid (97–100%, Matheson Coleman and Bell) which was distilled from boric anhydride[16] was thermostated at the solvolysis temperature for 30 min. The tosylate was dissolved in 25 μl of reagent grade methylene chloride in a vial and 1 ml of temperature-equilibrated formic acid was added. The mixture was then transferred from the vial to the conductance cell and the timer started. Conductance readings were taken on a Serfass conductivity bridge, Model RCM 15 B1 at intervals such that five to ten readings were taken during the first half-life. Rate constants were determined from a least squares fit of the kinetic data determined in the usual manner.[6b,c]

Formolysis. The tosylates **5a** and **5b** were dissolved in methylene chloride and anhydrous formic acid. In alternate experiments an equivalent amount of sodium formate was added. The reaction mixtures were allowed to react at 60° for 10 half-lives and then cooled to room temperature. Water was added and the solvolysis mixtures were extracted with methylene chloride. The organic extracts were washed three times with water and dried over sodium sulfate. Evaporation of the methylene chloride gave quantitative yields of formates which were crystallized from ether–pentane.

The formate **7** derived from the *exo*-tosylate **5a** melted at 109–110°; the formate **8** derived from the *endo*-tosylate **5b** melted at 136–137.5°.

(9) S. Winstein and K. C. Schreiber, *J. Amer. Chem. Soc.*, 74, 2171 (1952).

(10) (a) H. C. Brown and R. S. Fletcher, *ibid.*, 71, 1845 (1949); (b) *ibid.*, 73, 1317 (1951).

(11) P. D. Bartlett, *Bull. Soc. Chim. Fr.*, [5] 18, 104C (1951).

(12) P. D. Bartlett, *J. Chem. Educ.*, 30, 22 (1953).

(13) H. C. Brown, I. Rothberg, P. von R. Schleyer, M. M. Donaldson, and J. J. Harper, *Proc. Natl. Acad. Sci. U. S.*, 56, 1653 (1966).

(14) H. C. Brown, *Chem. Brit.*, 2, 199 (1966).

(15) H. C. Brown and K. Takeuchi, *J. Amer. Chem. Soc.*, 90, 5268 (1968).

(16) H. I. Schlessinger and A. W. Martin, *ibid.*, 36, 1589 (1914).

The crystalline formates were saponified at room temperature in 1:1:1 ethanol–ether–water which contained 0.5% sodium hydroxide. After 1 hr the reaction mixture was extracted with ether and the ethereal extracts were dried over sodium sulfate and evaporated. The residue was chromatographed on grade III neutral alumina.

The *exo*-formate **7** produced starting *exo*-alcohol in 89% yield, mp 116–119° (lit.[5] mp 118–121°), which was converted to the starting tosylate **5a**, mp 116–121°, mmp 116–121°.

Saponification of the *endo*-formate **8** gave *endo*-18-hydroxy-4,5-tetramethylene[2.2]paracyclophane (**9**) which after chromatography on grade III neutral alumina followed by crystallization from hexane–acetone gave material melting at 129–130°. The crude alcohol was obtained in 91% yield.

Anal. Calcd for $C_{21}H_{24}O$: C, 86.25; H, 8.27. Found: C, 86.36; H, 8.33.

18-Oxo-4,5-pentamethylene[2.2]paracyclophane (10). *endo*-18-Hydroxy-4,5-pentamethylene[2.2]paracyclophane (**9**) (0.90 g, 3.1 mmol) was dissolved in 30 ml of acetone and 15 ml of ether at 0°. Chromium trioxide (0.30 g, 3.0 mmol) was dissolved in 0.9 ml of water and 0.3 ml of sulfuric acid. This solution was added slowly to the solution of alcohol **8** at 0–5° over a 15-min period. After the addition was completed, the reaction mixture was maintained at 0–5° for 30 min. The reaction mixture was then diluted with water; the organic phase was extracted, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel. A mixture of 3:7 ether–hexane eluted ketone **10** (0.4 g, 72%). Recrystallization from petroleum ether–ether gave product melting at 122–124°.

Anal. Calcd for $C_{21}H_{22}O$: C, 86.85; H, 7.64. Found: C, 86.60; H, 7.43.

γ-[2.2]Paracyclophanoylbutyric acid methyl ester (12) was prepared from 43.8 g of aluminum chloride, 14.36 g of glutaric anhydride, and 20.83 g of [2.2]paracyclophane in 400 ml of methylene chloride according to the previously published procedure for β-[2.2]paracyclophanoylpropionic acid.[17] The crude acid was converted to the methyl ester by refluxing for 1.5 hr in methanol containing a small amount of sulfuric acid. The reaction mixture was diluted with water, and the ester **12** was extracted with ether. The ethereal solution was washed with water until neutral, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel. The ester **12** was eluted after unreacted [2.2]paracyclophane in 47% yield (10.5 g) with 1:4 ether–petroleum ether. Three recrystallizations from petroleum ether–ether gave material of mp 88.5–89.5°.

(17) D. J. Cram, C. K. Dalton, and G. R. Knox, *J. Amer. Chem. Soc.*, **85**, 1088 (1963).

Anal. Calcd for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.39; H, 7.16.

δ-(4-[2.2]Paracyclophanyl)valeric Acid (13). Ester **12** (3.0 g, 8.9 mmol) was saponified to the corresponding acid by refluxing for 10 min with an equal weight of sodium hydroxide in 40 ml of 1:1 ethanol–water. The aqueous solution was extracted with ether, then made acidic by dropwise addition of concentrated hydrochloric acid. The organic acid was extracted from the aqueous acidic solution with ether. The ethereal extracts were dried over sodium sulfate and evaporated to give 2.7 g (94%) of δ-[2.2]paracyclophanoylbutyric acid, mp 97–99°. Wolff–Kishner reduction of this acid and esterification were carried out as described previously for δ-[2.2]paracyclophanylbutyric acid methyl ester.[5] The ester was purified by chromatography on silica gel. It was eluted with 3:17 ether–petroleum ether as an oil. The ester was saponified as described above. The product acid **13** was isolated as a solid from an aqueous acidic solution (5.0 g, 58%, mp 78–80°). Recrystallization from petroleum ether–ether produced material, mp 92–94°.

Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 82.06; H, 7.82.

17-Oxo-4,5-pentamethylene[2.2]paracyclophane (14). Polyphosphoric acid (16.0 g) and acid **13** (1.2 g, 3.9 mmol) were allowed to react in a flask protected with a drying tube for 1.5 hr at 75–80°. The reactants were mixed vigorously every 15 min. Ice water was then added to the reaction mixture and it was then extracted twice with ether. The ethereal extracts were washed with water and saturated sodium bicarbonate solution. The ethereal solution was dried over sodium sulfate, then evaporated. The residue was chromatographed on silica gel. Ketone **14** was eluted with 4:1 hexane–ether in 75% yield (0.7 g). Recrystallization from ether gave material melting at 120–122°.

Anal. Calcd for $C_{21}H_{22}O$: C, 86.85; H, 7.64. Found: C, 86.78; H, 7.64.

4,5-Pentamethylene[2.2]paracyclophane (11) was prepared by Wolff–Kishner reduction of **14** as previously described for δ-[2.2]-paracyclophanylbutyric acid methyl ester.[5] Hydrocarbon **11** was extracted from the aqueous reaction mixture with ether. The ethereal extracts were washed with water until neutral, dried over sodium sulfate, and chromatographed on silica gel. Hydrocarbon **11** was eluted with hexane in 75% yield. Recrystallization from ethanol followed by sublimation at 85° (0.2 mm) gave material, mp 118–119°. The same procedure applied to ketone **10** also gave a 75% yield of **11**, mmp 118–119°.

Anal. Calcd for $C_{21}H_{24}$: C, 91.24; H, 8.76. Found: C, 91.12; H, 8.77.

Acknowledgment. We are indebted to Union Carbide for generous gifts of [2.2]paracyclophane.